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EDITORIAL

Tumor initiating cells in pancreatic cancer: A critical view

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Abstract

Emerging evidence points to the existence of pancreatic cancer stem cells (CSC) as the culprit in the initiation, maintenance, metastasis, and treatment resistance of pancreatic cancer. The existence of such a cell population would have an important impact on the design of novel therapies against this devastating disease. However, no *in vivo* validation or rebuttal of the pancreatic CSC hypothesis exists. Major backlashes in the discussion on CSC are firstly, the confusion between the terms CSC and cell of origin of pancreatic ductal adenocarcinoma (PDAC), secondly the ambiguity of the cell of origin itself and thirdly, the fact that the CSC hypothesis is based on cell sorting and xenografting experiments; the latter of which often precludes solid conclusions because of the lack of a natural microenvironment and differences in drug delivery. Nonetheless, recent studies in other cancers partially support the CSC hypothesis by demonstrating a link between epithelial-to-mesenchymal transdifferentiation/transition (EMT) and CSC properties. Such a link is again open to dispute as EMT is a reversible process which is highly dependent on major oncogenic pathways in PDAC [e.g. K-Ras, transforming growth factor-β (TGF-β)] rather than on presumed cancer stem cell pathways. Hence, the available evidence does not robustly support the CSC concept in PDAC and a thorough validation of this hypothesis in well-defined genetically engineered mouse models of pancreatic cancer is required.

Key words: Pancreatic cancer; Cancer stem cell; Tumor initiating cells; Mouse models

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INTRODUCTION

Pancreatic ductal adenocarcinoma (PDAC) is one of the most lethal cancers of the gastrointestinal tract with less than an overall 5-year survival rate of 5%. It is well known that human tumors including PDAC display significant heterogeneity in their respective cell populations. Based on normal hierarchical tissue architecture, the cancer stem cell hypothesis (CSCs) has been developed which suggests that only a specific subset of cancer cells in each tumor is responsible for initiation, maintenance and metastasis[1]. Specifically, the concept implies that a small number of stem or tissue-specific progenitor cancer cells give rise to the terminally differentiated or more committed progeny constituting the bulk mass of cancer, while at the same time these cells also maintain a process of self-renewal[2]. Therefore, following the first characterization of CSCs in acute myeloid leukemia (AML), the identification of pancreatic cancer stem cells was also reported[3,4]. However, a validation of the hypothesis, especially in the context of pancreatic cancer, does not exist. Confusion also derives from imprecise use of the terms "cancer stem cells" and "cell of origin" in PDAC which implies that cancer cells derive from normal tissue stem cells. This is of particular importance

in the development of PDAC because the cell or the cellular compartment of origin (i.e. ductal, acinar, centroacinar, endocrine, stem cells) is a subject of controversy. Genetically engineered mouse models of pancreatic ductal adenocarcinoma have made use either of mainly embryonically active, pancreas-specific promoters such as pdx1 or p48 (with specificity towards the exocrine pancreatic cellular compartment) or of inducible constructs driven by, for example, elastase expression to allow for Cre-recombination. Because neither a ductal- nor a centroacinar-specific promoter has been available so far, the cell of origin of PDAC remains obscure. However, initial data from genetically engineered mouse models have suggested that centroacinar cells which are considered to be pancreatic progenitor cells may be the cell of origin of PDAC. In a seminal paper, it has been shown that de-regulation of key pathways (e.g. PI3-K) in centroacinar cells might have contributed to the initiation of mouse PDAC[5,6]. Recently, some reports have argued that adult acinar cells can actually be transformed into pancreatic intraepithelial neoplasia and also into invasive adenocarcinoma , in the presence or in the absence of (chronic) inflammation[7-9]. These papers demonstrate that at least a subset of adult, differentiated cells is readily transformable into (pre-) malignant cells, suggesting that, if existing, a "pancreatic cancer stem cell" is rather derived from a differentiated compartment than from undifferentiated pancreas stem cells.

PANCREATIC CANCER STEM CELLS

So far, the CSC theory in pancreatic cancer largely relies on studies from FACS cell sorting according to the expression of specific "stem-cell" markers (CD133 or CD44/CD24/ESA) followed by xenografting of these cells into immune-compromised mice. Using such a system, a recent study reported that the combined blockade of so-called pancreatic CSC self-renewal pathways and standard chemotherapy eliminated the presumed pancreatic CSCs and resulted in prolonged survival of the transplanted mice[10]. Methodologically, this may not be an appropriate system for testing the CSC theory mainly because xenotransplantation itself has a number of disadvantages. For example, it does not provide the kind of real microenvironment which is usually required for the growth of pancreatic cancer cells[11-14]. Furthermore, drug delivery in xenograft PDAC models has been shown to be completely different than in genetically engineered mouse models[15], underscoring the difficulties in interpreting these results. Thus, the scarcity of so-called "tumor initiating cells" (i.e. CD133+ or CD44+CD24+ESA+) in human PDAC might in fact reflect the scarcity of human tumor cells that can readily adapt to growth in a foreign (mouse) milieu. The non-transplantable human PDAC cells may simply lack critical features for obtaining stromal support in the foreign microenvironment, such as responsiveness to mouse cytokines or chemokines that attract the cells to a nurturing niche rather than "stem-cell" properties[16,17]. Indeed, results from mouse leukemia and lymphoma challenge the general applicability of the cancer stem cell hypothesis to solid tumors because a substantial proportion of cancer cells can seed tumors in syngeneic animals and no functionally distinct subpopulation is evident[18,19]. It has recently also been shown that randomly selected single cells derived from mouse lung or breast cancer cell lines were able to produce tumors after allografting into histocompatible mice[20]. Furthermore, CD133 which is employed as a marker for (pancreatic) CSC is also expressed by endothelial cell precursors which were shown to be capable of enhancing growth of transplanted human cancer cells[21] Thus, using CD133 as a marker to isolate pancreatic cancer stem cells always carries the risk of enriching such a cell population.

EPITHELIAL-TO-MESENCHYMAL TRANSDIFFERENTIATION IN PANCREATIC CANCER

Recent evidence suggests that epithelial-to-mesenchymal transdifferentiation/transition (EMT) in PDAC marks an aggressive and, due to the expression of markers of CSC, a more "cancer stem cell-like" phenotype[22-24]. Accordingly, it has also been shown that highly metastatic pancreatic CSCs loose expression of the epithelial cell marker cytokeratin[3] illustrating a potential link between EMT and the cancer stem cell hypothesis. However, such a link may rather be a side-effect than a true effect since EMT is a reversible process that can be induced by various stimuli [e.g. transforming growth factor (TGF-β)] in the tumor microenvironment[25]. It is likely that in the stepwise malignant transformation process, pancreatic cancer cells have gained an ability to adjust their differentiation status to given environmental influences. This hypothesis seems to be supported by a recent report showing that pancreatic cancers can be divided into *K-ras*-dependent and -independent tumors. A comparison of these two classes of cancer cells revealed a gene expression signature in *K-ras*-dependent cells that was associated with a well-differentiated epithelial phenotype[26]. However, no changes in CSC marker expression has been reported after induction of EMT in such *K-ras*-dependent pancreatic cancer cells. Thus, the CSC "population" may also be considered as a transient state of the parental cancer cells which again would argue against the central concept of the cancer stem cell hypothesis.

CONCLUSION

Though the determination of the validity of the pancreatic CSC hypothesis would have an important impact on the design of novel therapies, the available evidence does not robustly support the CSC concept in PDAC. Therefore, we suggest analyzing the concept in well-defined genetically engineered mouse models of pancreatic cancer with the sole aim of eradicating the hypothesized minor population of CSC. Such experiments would determine

whether ablation of this presumed population of tumor-initiating cells has an effect on the development and potentially also the progression of the tumor.

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